REMARKS

Applicants respectfully traverse the final rejection of claims 1-63 as obvious over the combination of Bovicelli et al., Cicala et al., Holland et al., and Yang et al. (J. Org. Chem., 1998 or U.S. 5,763,623).

The instant invention relates to a method of ketone-catalyzed β-selective epoxidation of Δ^5-unsaturated steroids, and in particular a method of producing mostly 5β,6β steroid epoxides. Those skilled in the art wish to study specifically the 5,6-β steroid epoxides, but they have not been well studied because, unlike the alpha isomers, they are difficult to synthesize with high selectivity. Applicants acknowledge that the epoxidation of Δ^5-unsaturated steroids with dioxiranes or ketones as catalysts was well-known in the art; but such prior art reactions produced unpredictable ratios of 5,6-β to α stereoisomers. Prior to the present invention, it was not known how to choose specific dioxiranes/ketones and/or Δ^5-unsaturated steroids that would yield mostly the 5,6-β steroid epoxides. Thus, those skilled in the art did not know how to choose specific combinations of selected ketones or dioxiranes and/or selected Δ^5-unsaturated steroids would produce mostly 5β,6β steroid epoxides.

Applicants' invention is the discovery that high β-selectivity can be achieved by increasing the steric size of either the α-substituents of the dioxiranes, whether added as the dioxirane or generated in situ from the corresponding ketone; or, by increasing the steric size of the 3-α substituents of Δ^5 unsaturated steroids (specification, paragraph [0018]). Specifically, applicants have discovered that (1) epoxidation of Δ^5-unsaturated steroids with ketones of formula I, or the corresponding dioxiranes of formula VI, will result in mostly 5,6-β steroid epoxides, as recited in independent claims 1 and 26,

respectively; (2) epoxidation of Δ^5-unsaturated steroids that specifically incorporate 3-α-substituents will produce mostly 5β,6β steroid epoxides when the epoxidation reaction is carried out with a dioxirane or ketone as catalyst, as recited in independent claims 12 and 32, respectively; (3) epoxidation of Δ^5-unsaturated steroids of formula XI with ketones of formula XII will give mostly 5β,6β steroid epoxides, as recited in independent claim 42; and (4) epoxidation of Δ^5-unsaturated steroids of formula XIII with ketones of formulae XIV, XV, XVI or XVII will give mostly 5β,6β steroid epoxides, as recited in independent claim 53. See Tables 1-3 of the specification.

Prior to the instant invention, there has been no literature report of such high β-selectivity achieved in the epoxidation of Δ^5-unsaturated steroids. Prior art ketone-catalyzed epoxidation reactions have been unpredictable as to the ratio of β to α isomers produced. The selectivities of the claimed reactions have provided a much needed breakthrough in the ability to synthesize specifically the biologically significant 5β,6β-steroid epoxides (specification, paragraph [0101]).

It is respectfully submitted that the rejection of these claims under 35 USC 103 is based on certain misstatements of fact in the Office Action, which will now be addressed.

The Examiner has stated that "The issue is not whether the prior art teaches the selection of particular substrates and reactants but whether the prior art makes obvious said combination/selection." (Office Action p. 3) Applicants respectfully disagree. The issue is not whether the selection or combination is obvious to conduct *any* epoxidation reaction, but whether it is obvious that the claimed selection of substrates and reactants would yield *mostly the 5β,6β-steroid epoxides*, as specifically recited in each of the independent claims 1, 12, 26, 32, 42 and 53. This is a significant limitation in the claims

that cannot be ignored in determining patentability. In re Wilson, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art.") The issue is not whether there is a "reasonable expectation that *any* 5-ene steroid derivative would undergo epoxidation with the production of the corresponding 5,6-epoxy compounds", Office action, page 2, emphasis added, but whether the 5,6-epoxy compounds so produced would be mostly the 5,6-*β* epoxy compounds. In determining patentability, the standard is not whether it would have been obvious to try the claimed combinations, but whether it would have been obvious that the claimed combinations *would succeed* in producing the desired result, namely, a product of mostly the 5β,6β-steroid epoxides.

In this case, it would not have been obvious to one skilled in the art that the claimed combinations would have succeeded in producing mostly 5β,6β-steroid epoxides.

Turning first to independent claims 1, 26, and 42, each of these claims recites the epoxidation of Δ^5 unsaturated steroids with specifically selected ketones or dioxiranes, to give a product mostly 5β,6β-steroid epoxides. It would not have been obvious to one skilled in the art that the particular ketones and dioxiranes recited in these claims would have succeeded in producing the claimed *stereochemical* result. The applicants agree with the Examiner that it is obvious that (a) dioxiranes are useful oxidants; and (b) 5-ene steroids undergo epoxidation in the presence of an oxidant (office Action, page 4, line 21 – page 5, line2). But applicants do not agree that it is obvious that (c) the epoxidation of 5-ene steroids in the presence of a dioxirane results in the production of mostly the corresponding *5β,6β*-epoxide derivative (Office Action, p. 5, lines 1-3), because the prior art shows to the contrary. Other researchers at about the same time reported other

epoxidation reactions of 5-ene steroids that gave mostly the alpha isomer. For example, Marples, et al., Tetrahedron Letters, Vol. 32, No. 4, pp. 533-536, 1991 (submitted with Information Disclosure Statement in this application, see also specification paragraph [0007]), reported that epoxidation of Δ^5-unsaturated steroids using dioxiranes generated from cyclohexane and ethyl pyruvate produced mostly the α-epoxides, not the β-epoxides. See, Marples, p. 535, Table 1, entries 2 and 5, wherein the α:β epoxide ratio was reported as 55:45 and 64:36 respectively. According to Marples, even acetone gave an α:β epoxide ratio of about 50:50 (id., entry 1). The inventors' own work, reported in the specification at Table 1, entries 1 and 3, demonstrated that epoxidation of 3β-substituted 5-ene steroids catalyzed by ketones other than those claimed gave more of the α-epoxides than the β-epoxides.

Thus the Examiner's statement (Office Action, p. 5, lines 3-5) that "The skilled artisan would have the reasonable expectation that *any* dioxirane would be useful in the epoxidation of *any* 5-ene steroid with the production of *mostly the 5β,6β*-epoxides" (emphasis added) is respectfully traversed. One skilled in the art would not have had such an expectation, nor would such an expectation have been reasonable, because *any* dioxirane reacting with *any* 5-ene steroid would *not* necessarily produce mostly the 5β,6β-epoxides, as is seen when the prior art is considered as a whole.

Bovicelli and Cicala do not teach to the contrary. Bovicelli teaches epoxidation using only one dioxirane, namely, dimethyl dioxirane, with four different steroid structures, only one of which is a 5-ene steroid (Bovicelli, Scheme I, second reaction). Similarly, Cicala reports four different reaction schemes, and all involve allylic alcohols; only substrate 4 is a 5-ene steroid. These two reported reactions, when taken together

with the Marples reference and the inventors' work discussed above, and the other prior art teachings reported in the specification paragraphs [0005]-[0011], do not teach or suggest to one skilled in the art the stereoselectivity that applicants have achieved in generating mostly the 5β,6β epoxides, as recited in the claims

Further, even if it were true that it were obvious that increases in the yield of the end product could be obtained by changes in the reaction conditions (Office Action, page 5, lines 5-7), that is beside the point. The point of the invention is not to increase the overall yield of the reaction, but to increase the proportion of the beta isomer to the alpha isomer. The prior art teaches nothing about changing reaction conditions to change the proportion of the isomers in the reaction product. Thus, the prior art taken as a whole did not teach or suggest that the particular ketones and dioxiranes listed in these claims would give mostly the 5β,6β-steroid epoxides.

Considering next independent claims 12, 32, and 53, and the claims that depend from these claims, claims 12, 32, and 53, each recites the epoxidation of a 3α-substituted Δ^5-unsaturated steroid using ketones or dioxiranes. *None of the cited prior art references teaches or suggests the ketone-catalyzed or dioxirane-mediated epoxidation of a Δ^5-unsaturated steroid with a substituent in the 3α-position*; i.e., to applicants' knowledge there is simply no such report in the literature. And certainly none of the prior art references, taken alone or in any combination, teaches or suggests that the presence of a substituent in the 3α-position on a Δ^5-unsaturated steroid will lead to an epoxidation reaction product of *mostly 5β,6β-steroid epoxides*. Applicants agree with the Examiner that "epoxidation of 3α-substituted steroid in the presence of an oxidant is known in the art" (Office Action page 4, lines 8-9). However, that does not mean that *any* oxidant

including a dioxirane will produce mostly the 5,6-β epoxide just because the oxidant can produce mostly the 5β,6β-epoxide by epoxidation of *3β*-substituted steroids, as Bovicelli and Cicala' results discussed before. For example, the Holland reference teaches epoxidation of one 3α-substituted steroid with a peracid, *m*-chloroperoxybenzoic acid, to give exclusively α-epoxide, not β-epoxide (See: Journal of Organic Chemistry Vol. 48, No. 18, pp. 3134-3136, 1983). The inventors' own work, reported in the specification at Table 3, entry 1, showed that epoxidation of one 3α-substituted steroid with *m*-chloroperoxybenzoic acid gave a ratio of 9.5:1 α to β-epoxide. Applicants agree with the Examiner that the skilled artisan would have the reasonable expectation that "3α-steroid derivative would undergo epoxidation in the presence of a dioxirane" (Office Action page 4, lines 10-11), but one skilled in the art would have no expectation that the product would be *mostly the 5β,6β-epoxide*, as opposed to the alpha epoxide. Similarly, applicants do not contest that "based on the teachings of the cited prior art, epoxidation of any 5ene steroid including the 3α-derivatives, would be prima facie obvious" (Office Action, page 4, lines 18-20). But it would not have been obvious that the *result* would have been mostly the *5β,6β-epoxides*, as opposed to the alpha isomers. Therefore, claims 12, 32, and 53 specifically relating to the epoxidation of a 3α-substituted Δ^5-unsaturated steroid using a ketone or dioxirane to produce mostly the *5β,6β-epoxides* cannot be obvious over the prior art.

Turning next to claims 11, 25, 31, and 41, each of these claims recites that the epoxides of the reaction product have at least about 5:1 β/α epoxide ratio. Nothing in the prior art teaches or suggests that such a ratio can be achieved, with any 5-ene steroid or

any dioxirane or ketone. Accordingly, each of these claims also is non-obvious over the prior art.

For the foregoing reasons, a Notice of Allowance is respectfully requested.

The applicants' undersigned representative wishes to thank the Examiner for the courtesies extended during the telephone interview earlier today. As agreed in the interview, it is requested that the Examiner call the undersigned representative before any further action is taken in this case.

Respectfully submitted,

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